Efficacy of bazedoxifene, pre-biphosphonate sequential therapy for osteoporosis and the patient profile for bazedoxifene

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Summary
Osteoporosis is a gendered disease, being especially prevalent in postmenopausal women due to the sharp drop in levels of endogenous oestrogens. The interest in, and concern for, this pathology has resulted in the development of ever more efficacious and safe new drugs. Bazedoxifene (BZA) is a new third generation SORM, recently launched on the European Union market for the treatment of postmenopausal osteoporosis in women at high risk of fracture. BZA, at a dose of 20 mg/day, has shown a significant effect on the prevention of loss of bone mass in healthy postmenopausal women with low or normal bone mineral density. In a pivotal study aimed at osteoporotic women, BZA has reduced by 42% (p<0.05) the risk of vertebral fracture at three years in comparison with a placebo; this effect is maintained over five years. In addition, it has been shown in a post hoc analysis, in a group of women at high risk of fracture, to diminish the risk of non-osteoporotic fractures by 44% more than 60 mg of raloxifene (p=0.05). Its anti-fracture potency and its strong uterine antioestrogenic effect makes bazedoxifene especially indicated in recently postmenopausal women with osteoporosis and risk of fracture.

Key words: Bazedoxifene, Antifractural potency, SORMS, Osteoporosis, Sequential therapy.
Introduction
The interest in, and concern about, osteoporosis has resulted in the acquisition of greater knowledge of its epidemiology, achieving advances in diagnostic tools and the discovery of ever more efficacious and safe new drugs. In terms of the drugs, there are currently multiple options, among which are included the bisphosphonates and the selective oestrogen receptor modulators (SORMs: raloxifene (RLX) and bazedoxifene (BZA)), the oestrogens calcitonin, parathormone (PTH) and strontium ranelate. With the exception of the oestrogens, the antifractural effects of all these medicines has been demonstrated in women with a densitometric diagnosis of osteoporosis. All this necessitates an individualised therapeutic indication depending on the benefit-risk profile of each patient.

The SORMs represent a class of drugs with ever more numerous compounds, characterised by acting as agonist/antagonist of oestrogen receptors (OR) in a tissue-specific way. This pharmacological profile may offer an opportunity to obtain favourable oestrogenic effects, while avoiding any negative effects of them on breasts and endometrium. The SORMs have been shown to have great value in breast cancer. They have also been shown to be efficacious in the prevention and treatment of osteoporosis and in improving lipid metabolism, and there are other possible benefits which are being studied, such as as a treatment for vaginal atrophy. This versatility of the SORMs is due to the capacity of each of them to produce a different conformational change in the oestrogen receptors α and β, and with this, ultimately, to stimulate or block the activity of the transcription genes for the oestrogens.

The different SORMs exert a different affinity and competition for the bond to the oestrogenic receptors and determine a different genetic expression. The evidence suggests that each SORM should be studied, and its clinical response evaluated, independently.

The two SORMs currently most used are tamoxifen, which is used for the prevention and treatment of breast cancer, and raloxifene, indicated for the treatment and prevention of postmenopausal osteoporosis, and for the prevention of breast cancer in the US. Both SORMs have positive effects on the lipids, but are associated with an increased risk of venous thromboembolism and hot flushes. In addition, tamoxifen increases the risk of cancer of the endometrium. On the other hand, none of these SORMs have shown a preventative effect on non-vertebral fractures.

Therefore, of any new SORM it is necessary to ask which has the best efficacy, or the best safety, or both, knowing that the ideal SORM is one which prevents vertebral and non-vertebral osteoporotic fractures, which serves as primary or secondary prevention of breast cancer, and which may have additional benefits regarding cardiovascular risk. This ideal SORM would not increase the risk of either hyperplasia, or endometrial adenocarcinoma, nor venous thromboembolisms or hot flushes.

Although it is very difficult to find this ideal SORM, the new SORMs are a step forward, based on preclinical selection criteria and data on the clinical response in relation to efficacy and safety.

Up until now, RLX has been the only SORM in the market approved for the treatment of osteoporosis. Now we can also count on bazedoxifene (BZA), a new generation SORM, which has completed its clinical development and has been approved by the European Medicines Agency (EMEA) for the treatment of postmenopausal osteoporosis in women with a high risk of fractures.

Efficacy of bazedoxifene
BZA is a SORM derived from the indoles, with phenyl rings which act as the site for bonding to the receptor. They bond strongly with both types of oestrogenic receptor, alpha and beta, but with the bond to the alpha oestrogen receptors being clearly stronger.

The first preclinical studies showed that they did not stimulate the proliferation of the MCF-7 mammary cell line, and even suppressed, dose-dependently, the proliferation induced by 17 beta estradiol. In animal studies treatment with BZA reduced the markers for remodelled bone and prevented the loss of bone mass. What appeared to be especially interesting was that it protected the increase in uterine weight produced by the oestrogens in immature rats. The potency of BZA over the inhibition of uterine weight and on the stimulation of the mammary gland cells produced by the oestrogens is higher than that found with other SORMs, such as raloxifene and lasofoxifene.

Pharmacokinetics and pharmacodynamics
BZA has been demonstrated in healthy postmenopausal women to have a half life of 28 hours, with a maximum blood concentration at within 1-2 hours of taking the dose. The main route of excretion (85%) is through the faeces. Its administration to patients with hepatic insufficiency may elevate the drug’s blood concentration, for which reason its use is not recommended in these cases, as well as in severe renal insufficiency, since, although the principal mode of excretion is through the faeces, it is also partially excreted in the urine.

Bazedoxifene increases concentrations of sex hormone-binding globulin SHBG and thyroxine-binding globulin TBG. It does not metabolise through cytochrome P450, which means that important this enzyme neither induces nor inhibits the activities of the isoenzymes. In vitro analyses suggest that bazedoxifene does not interact with other drugs which metabolise by means of cytochrome P450, and therefore no significant pharmacological interactions have been described.

No pharmacokinetic differences have been observed in relation to race.

The lowest efficacious dose
The two phase 2 clinical studies have shown a clearly significant reduction in markers for remodelled bone with BZA, compared with a placebo,
and even with a dose of only 5 mg a day of BZA, this reduction being dose-dependent. On the other hand, in this clinical phase it was possible to confirm that a dose of 20 mg/day of BZA was the lowest dose which provided the best efficacy profile with a good endometrial and mammary safety profile.

**Study of prevention**

A phase 3 clinical study of osteoporotic prevention has been carried out of two years duration, including 1,583 healthy postmenopausal women with low or normal bone mineral density (BMD), with the triple of objective of looking at efficacy and safety, comparing the lowest efficacious dose and comparing it with raloxifene RLX.

In this study the women received daily doses of BZA of 10, 20 and 40 mg, 60 mg of raloxifene or a placebo, and all of them took 600 mg of calcium element daily during the two years of the study (Table 1). Both the three doses of BZA and the dose of RLX had the same efficacy in the prevention of loss of bone mass measured as BMD in the lumbar spine, hip, femoral neck and femoral trochanter. Already at 6 months, the three doses of BZA demonstrated a significant preventative effect on the loss of BMD compared with the placebo. The differences in average percentages of BMD in the lumbar spine with respect to the baseline at 24 months with 10, 20 and 40 mg of BZA, in comparison with the placebo, were 1.08 ± 0.28%, 1.41 ± 0.28% and 1.49 ± 0.28% respectively (with statistical significance of p < 0.001 for all).

### Table 1. Clinical characteristics of the prevention of osteoporosis at 2 years

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Multicentric, double blind, randomised, compared with active product (raloxifene) and placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main selection criteria</td>
<td>Healthy women ≥ 45 years and ≥ 1 year of postmenopause. Women between 1 and 5 years of postmenopause should have ≥ 1 risk factor for OP</td>
</tr>
<tr>
<td>Treatment groups</td>
<td>BZA 10 mg (n= 292); BZA 20 mg (n= 288), BZA 40 mg (n= 290); RLX 60 mg (n= 280), placebo (n= 284)</td>
</tr>
<tr>
<td>Average age</td>
<td>58 years</td>
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<tr>
<td>Half of DMO in lumbar column (T Score)</td>
<td>-1.12 to -1.24</td>
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### Table 2. Characteristics of pivotal study at 3 years

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Multicentric, double blind, randomised, compared with active product (raloxifene) and placebo</th>
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<tbody>
<tr>
<td>Main selection criteria</td>
<td>Generally healthy women aged between 55 and 85 years and ≥ 2 years of postmenopause with OP (BMD in the range for OP or vertebral fracture confirmed by radiography)</td>
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<tr>
<td>Treatment groups</td>
<td>BZA 20 mg (n= 1,886); BZA 40 mg (n= 1,872), RLX 60 mg (n= 1,849); placebo (n= 1,885)</td>
</tr>
<tr>
<td>Average age</td>
<td>66 years</td>
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<tr>
<td>Half of DMO in lumbar column (T Score)</td>
<td>-2.4</td>
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Other interesting data from the study were that at three months, both the women on BZA and those on RLX showed a significant reduction in levels of markers for remodelled bone (blood osteocalcin and telopeptide C), compared to those found in the placebo group (p< 0.001), and this effect continued during the whole study. In addition, BZA showed a positive effect on the lipid profile, with a significant reduction being found in levels of total cholesterol (-3.75%) and cLDL (-3.6%), and a significant increase in cHDL (5.10%), in comparison with the placebo.

Pivotal study

The pivotal phase 3 clinical study was designed to determine the efficacy and safety of BZA in the prevention of fractures in postmenopausal women with osteoporosis (Table 2). In this study, the women received daily treatment with BZA at 20 or 40 mg, 60 mg RLX, or a placebo, all supplemented with 1,200 mg daily of calcium and 400-800 UI of vitamin D.

BZA significantly increased BMD and reduced the levels of markers for remodelled bone (osteocalcin and telopeptide C), compared with the placebo (p< 0.001). The incidence of new vertebral fractures at 3 years, which was the main objective of the study, saw a clearly significant reduction with 20 mg of BZA (a reduction after 3 years of 42%), with 40 mg of BZA (a reduction after 3 years of 43%), and 60 mg of RLX (a reduction after 3 years of 42%), in comparison with the placebo. All these reductions with active treatments were statistically significant (p< 0.05) with respect to the placebo (Figure 1). In terms of the % of fracture, at three years they were 2.3, 2.5, 2.3 and 4.1% with BZA at 20 mg, BZA at 40 mg, 60 mg of RLX and the placebo, respectively. The effect of the treatments was similar in women with or without previous fractures.

The incidence of non-vertebral fractures was similar at three years in the group with 20 mg BZA (5.7%), 40 mg BZA (5.6%), 60 mg RLX (5.9%) and the placebo (6.3%)14. However, in a post hoc analysis of a sub-group of women with a high risk of fracture, based on known risk factors (n=1,772), BZA at 20 mg showed a reduction in risk of non-vertebral fractures of 50% compared with the placebo (p= 0.02) and 44% with respect to 60 mg of RLX (p= 0.05) (Figure 1).

An independent reanalysis has been carried out of the fracture data of the whole population, using FRAX (the Fracture Risk Assessment tool), to estimate the probability of fracture at 10 years. The results of this analysis show that BZA reduces significantly the risk of all clinical fractures and morphometric fractures. Similar results were observed regarding the effects of BZA on non-vertebral fractures. Another conclusion has been that the effect of BZA increases according to an increase in the probability of fracture.

The positive effect of 20 mg of BZA in the lipid profile was of a reduction after three years from the baseline for total cholesterol of -3.8% (p<0.001) and of cLDL of -5.4% (p< 0.001), with a clear increase in cHDL of 5.1%. There were no changes in the triglycerides compared with the placebo group.

A total of 4,216 women were included in the extension study which lasted a further two years. The 60 mg RLX group finished at the fourth year, and the patients who were in the 40 mg BZA group...
were moved to the 20 mg group at the fourth year, constituting the 40/20 mg BZA group. The results, which were presented at 5 years, were in respect of the 20 mg BZA and 40/20 mg BZA groups, compared with the placebo group. The primary objective was to look at new vertebral fractures, and secondarily, at non-vertebral fractures.

At 5 years the incidence of new vertebral fractures was significantly lower in the 20 mg BZA (4.5%) and 40/20 mg BZA (3.9%) groups, than in the placebo group (6.8%), corresponding to a relative risk of 35% less (p=0.014) and 40% less (p=0.005), respectively (Figure 2). There were no significant differences in the study’s population in terms of non-vertebral fractures between 20 mg BZA (9.5%), 40/20 mg BZA (7.6%) or the placebo (9.0%). In the analysis of the high risk patients (T-Score in the femoral neck less than or equal to 3 and/or one or more moderate vertebral fracture or two or more light vertebral fractures; n=1,324), there was a reduction in incidence of 37% (p=0.06) and of 31% (p=0.16) (Figure 2) of non-vertebral fractures in the 20 mg BZA and 40/20 mg BZA groups in relation to the placebo group.

In conclusion, the values for the reduction in new fractures and, in a high risk sub-group, of non-vertebral fractures , were maintained throughout the two year extension, with the results at 5 years being similar to those at 3 years.

Sequential therapy for osteoporosis

A key clinical objective consists in identifying those patients with a high risk of presenting this disease. Osteoporosis is predictable and treatable, but the lack of alert signals before the appearance of a fracture means that few patients are diagnosed in early phases of the disease and treated efficaciously. Osteoporosis is the most significant risk factor, and the one with greatest predictive power, for fragility fractures (atraumatic fractures or those due to minimum trauma).

Knowledge of the risk factors is important for detecting those patients in whom it is most probable that the disease will appear. But the correction of those factors that are modifiable also has notable therapeutic implications.

When the bone mineral density and those risk factors for each woman are determined doctors are in a position to answer their patients’ queries about the level of risk of fracture and their obligation to promote changes in the patients’ life styles, to predict the use of health resources and carry out a minimum cost benefit analysis of the possible alternative interventions for the disease. The necessity of treating osteoporosis is justified by the reduction in risk of fractures by increasing bone strength with this intervention. A systematic review of 76 clinical trials and 24 meta-analyses confirm the efficacy of the treatment in the prevention of fracture in comparison with the placebo in women with low bone mass or osteoporosis.

Although there is no common agreement on which women should receive drug treatment, the majority of scientific societies have suggested that it is indicated in those who have already presented with fragility fracture before the presence of densitometric osteoporosis and when there is low bone mass and associated risk factors.

There are no fixed rules or established protocols in terms of the drug or regime to be used. The decision to start treatment and which type should be based on the necessity to reduce the risk of
fracture, taking into account in each specific case the following factors, in addition to BMD and other major risks: renal function, drug allergies, comorbidities, earlier treatments, contraindications, secondary effects of the drugs and costs. By doing this it is possible to establish the risks and benefits of a drug for each patient. In addition, it is recommended that the importance of improving adherence be considered. Treatment for osteoporosis, it being a chronic disease, needs to be used over a long period, which makes necessary the use of individualised measures and sequential treatments.

Sequential treatment consists in designing a strategy which will sustain a drug over a sufficient period of time in order to achieve its benefits with minimum risk and maximum adherence, in order to be able to later move onto another drug, or drugs, which achieve the same results. The undesirable effects of prolonged use of some drugs, dealing with the risk of fracture which we wish to prevent and data from clinical trials which support their use, as well as efficacy in relation to the age of the patient, will have to be taken into account. Drug treatment should not be static but should change over the lifetime of the woman, thus adapting to her clinical needs and metabolism over time.

In theory, the treatments could start to be used during the first postmenopausal years using drugs aimed at the physiopathology of the rapid bone loss produced by the increase in bone resorption as a result of the reduction in oestrogen (Figures 3, 4), the most appropriate drugs being hormone replacement therapy (HRT) in symptomatic women and the SORMs in asymptomatic women. Another possibility could be HRT for two or three years and then SORMs, or a combination of oestrogens with a SORM (TSEC). Subsequently, there is a period with an increase in resorption and a reduction in formation (Figures, 3,4), coinciding with over 10 years of postmenopause and with a greater risk of hip fracture, where drugs such as bisphosphonates or strontium ranelate have clearly shown their effectiveness. Finally, in women of more than 70-75 years of age, there is a significant reduction in formation (Figures 3, 4), where PTH could be indicated in cases at very high risk of fracture.

**Patient profile for bazedoxifene**

The most common, and frequently unnoticed, consequence of osteoporosis, is an increase in the risk of fracture, and most seriously, in mortality and morbidity. For this reason, the objective of treatment in osteoporosis is the prevention of new fractures, and in patients with fractures, in minimizing the symptoms, improving functionality and optimising quality of life. The knowledge of the greatest risk factors for fracture and bone loss will help the therapeutic approach.

On the basis of the initial consideration that bazedoxifene is indicated in the treatment of osteoporosis in postmenopausal women with an increased risk of fracture, in principal, it could be indicated for all those women with this condition and in whom there is no contraindication for its use. By assessing the specific characteristic and effects of the product, it is possible to profile those women to whom it would be expected to bring most benefit. Bazedoxifene has shown efficacy in osteopenic (average age 57.6) and osteoporotic (average age 65.9) women, which means that its indication could be around women with an increased risk of fracture in the first years after the menopause (natural or surgical). Taking into account the fact that the most frequently reported adverse effect is the presence of hot flushes, it does not seem sensible to indicate this treatment in their presence.

Bazedoxifene has shown efficacy both if there is a vertebral fracture, as well as in their absence. The women who get the most benefit from the drug treatment are those at risk of fracture and in whom has also been shown a reduction in fractures in any location.

In clinical trials bazedoxifene did not produce more adverse gastrointestinal effects than the placebo, so, another group which could benefit are patients with poor tolerance of other treatments (for example, gastrointestinal intolerance to bisphosphonates), and may be taken at whatever time of day, with or without meals, which makes it somewhat easier to establish a time of taking the dosage which matches the patient’s preference, avoiding the necessity of strict rules for timing, fasting or limitation of activities.
Other considerations to be taken into account are that BZA has an appropriate security and tolerance profile, a favourable lipid profile, a neutral effect on the breast and an antioestrogenic effect in the endometrium16, which helps good compliance. Thus, in clinical trials the rate of abandonment has been similar to the placebo13,14.

It is important to bear in mind that it is not the treatment of choice for patients with a personal history of venous thromboembolism or with a raised risk of presenting this pathology. Another indication comes from the evaluation of its cost-effectiveness. One of the most recent works has been to evaluate the binomial coefficient of the cost-efficacy of BZA vs a placebo in France, Germany, Italy, Spain, United Kingdom and Sweden26, form the public health perspective using the FRAX index16. The conclusions have been that the use of BZA can be economical from the point of view of cost-effectiveness, depending, as seems logical, on how high the risk of osteoporotic fracture is according to the FRAX index.

Bibliography